Remarks

Applicants' claims 1 and 38-93 are pending in the identified patent application directed essentially to a method for regulating, controlling or modulating aqueous humor secretion, comprising the step of administering to ciliary epithelial cells of the aqueous humor (either *in vitro* or *in vivo* in a test animal or a human patient), an effective secretion-modulating amount or an effective pressure-modulating amount of a pharmaceutical composition comprising a modulator of one or more antiports. In preferred embodiments, the one or more antiports are selected from the group consisting of a Na^+/H^+ exchanger and a Cl^-/HCO_3^- exchanger, although apparently the Examiner's rejections below address only Na^+/H^+ exchange inhibitors.

Applicants have amended and corrected several reference citations in the specification that were initially incorrectly reported, but that were correctly provided in Applicants' Information Disclosure Statement. Claims 1, 42, 43, 56, 69, 81 have also been amended. No substantive change has been made by amendment, and no new matter has been added to the application.

The Examiner has indicated that the information disclosure statement filed on June 20, 2002 fails to comply with the provisions of 37 CFR 1.98(a)(2) because a legible copy of each cited patent and non-patent reference was not provided with Applicants' submission. However, contrary to what was forwarded to the attention of the Examiner, all patent and non-patent references cited in Applicants' Form 1449 were attached thereto when it was initially received by the US Patent and Trademark Office.

As evidence that Applicants filed a complete Information Disclosure Statement and all cited references (1-58) on June 20, 2002, Applicants submit herewith a copy of the date stamped return receipt card which acknowledges receipt on June 20, 2002 by the U.S. Patent Office of Express Mail Label No. EL 92934051US, along with (1) Information Disclosure Statement, (2) IDS Transmittal, (3) PTO-1449 and (4) copies of cited references. Applicants also enclose herewith another copy of the 58 non-patent references (the patent references having already been procured by the Examiner), as originally filed on June 20, 2002.

In view of the foregoing, Applicants respectfully request all references be considered timely filed and that they be reviewed by the Examiner prior to further examination of this application. Should any reference cited therein be the basis for additional rejection, such

rejection should not be final, since the loss of the originally filed references and the lack of their availability to the Examiner was not within Applicants' control.

Response to the claim rejections under 35 USC §102.

The Examiner has rejected claims 1, 38-43 and 47-93 under 35 USC § 102(b) as anticipated by Drug Facts and Comparisons (1994). In making this rejection, the Examiner states that the cited reference teaches "timolol, a beta blocker, to be employed to reduce elevated and normal ocular pressure with or without glaucoma" thereby, in the view of the Examiner, inherently modulating the antiports, although such utility may not have been expressly recited. The Examiner has reached this conclusion based upon the premise that the mechanism of operation of timolol is taught by the cited reference "to be a reduction of aqueous production, and a slight increase in outflow facility." In view of this work, the Examiner has rejected Applicants' invention.

However, Applicants' in the Background of the Invention describe at page 3, lines 17-page 4, line 1, that

> "four primary classes of drugs are used: miotics (*e.g.*, pilocarpine, carbachol and acetylcholinesterase inhibitors); sympathomimetics (*e.g.*, epinephrine, dipivalylepinephrine and parn-amino clonidine); beta-blockers (*e.g.*, betaxolol, levobunolol and timolol); and carbonic anhydrase inhibitors (*e.g.*, acetazolamide, methazolamide and ethoxzolamide). . . . To date, the most effective medical therapies are aimed at reducing intraocular pressure by inhibiting or reducing the net rate of aqueous humor formation. This can occur either by blocking unidirectional secretion from stroma to the aqueous humor or by stimulating flow in the opposite direction." [citations omitted]

However, prior to Applicants' invention the mechanisms underlying slowing aqueous humor formation by the ocular ciliary epithelial bilayer have been poorly understood (see, e.g., Application page 5, lines 1-7; page 11, lines 10-19). Prior to the present invention such drugs were used to treat glaucoma by reducing the rate of flow of fluids into the eye.

To the contrary, at page 11, lines 20-26, Applicants teach:

> The present invention provides new understanding of the sodium/proton exchanger, and its functional relationship with the chloride/bicarbonate exchanger (the "antiports"), regarding the uptake of salts from the body into the PE cells. More particularly, identifying and characterizing a Na^+/proton exchanger as the antiport, permits strategies to be developed to use drugs at very low, focussed

concentrations for preventing, modulating or regulating intraocular pressure, most particularly for treating or reducing elevated intraocular pressure.

The Examiner's cited reference describes the use of timolol at 0.25% or 0.5% twice daily to effect 31% to 33% mean IOP reduction, but nowhere in the reference is the mode of the timolol operation suggested or indicated. As has been made clear throughout Applicants' disclosure, there are many ways of reducing IOP, typically by limiting the rate of flow of fluids into the eye, and timilol and other drugs may produce such an effect. Timolol may also reduce the rate of production of cyclic adenosine monophosphate. But the cited prior use of timolol to reduce IOP does not indicate a reduction of IOP by the methods in the present invention, and such methods are the subject of the invention – not simply reducing IOP by previously known methods. To be inherently provided by the prior art, the IOP reduction would have to be achieved by modulating one or more antiports as taught by Applicants' invention, as opposed to by previously known methods described in Applicants' background – which is missing from the Examiner's reference.

~~It was set forth in In re Oelrich, 212 USPQ 323, 326 (CCPA 1981) that inherency may~~ not be established by probabilities or possibilities. "The mere fact that a certain thing may result from a given set of circumstances is not sufficient [to establish inherency]." Id. Although Applicants recognize that the PTO lacks the resources to acquire, manufacture or test products, the Examiner may not reject Applicants' invention on the erroneous assumption that timolol *may* inherently reduce IOP by modulator of one or more antiports - not when IOP may also be reduced by so many other mechanisms. See also, Ex parte Skinner, 2 USPQ2d 1788, 1789 (BPAI 1987).

When examined, the cited the prior art fails to define every element of Applicants' invention, meaning that the cited references fail to anticipate the invention. Specifically, the cited reference fails to in any way suggest or teach administering to ciliary epithelial cells of the aqueous humor, an effective secretion-modulating amount of a pharmaceutical composition comprising a modulator of one or more antiports. Consequently, it is clear that the cited reference fails to anticipate Applicants' invention under 35 USC § 102(b) since there is no indication in the reference, nor does it teach Applicants' method of modulating aqueous humor secretion by modulating the antiports of the aqueous humor. Accordingly, Applicants respectfully request that the rejection under 35 USC § 102(b) be reconsidered and withdrawn.

Response to the claim rejections under 35 USC §103.

The Examiner has rejected claims 1, 38-41, 44-45, 49-50, 52-53, 55-63, 65-66, 68-76, 78-79, 8-87, 89-90 and 92-93 under 35 USC § 103 as obvious, over Burke (US Patent No. 5,215,99). In making this rejection, the Examiner states that although it fails to teach glaucoma, Burke teaches "methods and pharmaceutical compositions of Na^+/H^+ exchange inhibitors, which are employed to lower ocular pressure (IOP) and for the treatment of intraocular hypertension (increased intraocular pressure)." In addition, the Examiner states that "Na^+/H^+ exchange inhibitors, such as amiloride analogs, improve the ocular hypertensive profile of various alpha-2 agonists when co-administered with the alpha-2 agonist." Hence, the Examiner has rejected Applicants' invention.

However, contrary to the Examiner's comments, the cited reference, even when combined with other prior art cited by the Examiner fails to disclose, or even suggest, Applicants' invention. In fact, rather than teaching Applicants' claimed invention, Burke actual confirms the unmet need in the art for such an invention. In two different points in the patent Burke states that the Na^+/H^+ exchange inhibitors, by themselves, do not work to lower IOP. See last paragraph of column 1, lines 56-60 ("It has now been discovered that Na^+/H^+ exchange inhibitors . . . although substantially inactive by themselves in lowering IOP . . ." and at the bottom of column 6, lines 63-65 ("Administration of three concentrations (0.1, 0.3, 1%) of the Na^+/H^+ exchange inhibitor did not significantly alter IOP (FIG. 1)." Consequently, Burke does not teach the use of Na^+/H^+ exchange inhibitors by themselves, rather Burke claims a method of lowering IOP by a co-administration of a IOP lowering amount of an alpha-2 agonist and an amount of the Na^+/H^+ exchange inhibitor, amiloride or its analogs. Accordingly, Applicants' invention was not, at the time of the invention, obvious to one of ordinary skill in the art with any expectation of success, and the findings would have required undue experimentation.

Burke could not have taught Applicants' invention because testing in that patent was done in a rabbit. Although rabbits are indeed widely used for testing ophthalmic drugs, the aqueous humor dynamics are quite different from humans. Aqueous humor flows out of the eye largely through the series arrangement of trabecular meshwork and then Schlemm's canal in primates, including humans. This outflow pathway is known as the conventional outflow pathway. Tamm, Russell and Piatigorsky have specifically reported that the conventional outflow pathway of the mouse is much closer morphologically to the human than many other

non-primate model systems, such as the calf and rabbit eye (Tamm ER, Russell P, Piatigorsky J, "Development and characterization of an immortal and differentiated murine trabecular meshwork cell line," Invest. Ophthalmol Vis. Sci. 40:1392-1403 (1999)).

By comparison, Applicants' claimed invention is actually in direct opposition to the Burke claims, and Burke teaches away from the present invention. Applicants have unequivocally demonstrated that the independent application of each of 3 different direct specific blockers of Na^+/H^+ exchange, by themselves, lower IOP in the mouse (See also, Avila, MY, Seidler, RW, Stone, RA and Civan, MM, "Inhibitors of NHE-1 Na^+/H^+ exchange reduce mouse intraocular pressure," Invest. Ophthalmol. Vis. Sci. 43:1897-1902 (2002)).

In part, the difference between the effectiveness of mouse verses the rabbit as a test animal for human aqueous humor dynamics, may arise from the site or sites of action of the blockers of Na^+/H^+ exchange. Applicants tested the effects of the blockers of Na^+/H^+ exchange based upon in vitro evidence that Na^+/H^+ exchange is important in aqueous humor inflow (production by the ciliary epithelium). Subsequently, they found that blockers of Na^+/H^+ exchange also have a prominent effect on increasing outflow (Avila, MY, Mitchell, CH, Stone, RA and Civan, MM, "Noninvasive assessment of aqueous humor turnover in the mouse eye. Invest. Ophthalmol. Vis. Sci. 44:722-727 (2003)). Although not intended to limit their invention, Applicants hypothesize that the enhancement of outflow may arise from the action of blockers of Na^+/H^+ exchange to shrink the trabecular meshwork cells (Mitchell, CH, Fleischhauer, JC, Stamer, WD, Peterson-Yantorno, K and Civan, MM, "Human trabecular meshwork cell volume regulation," Am. J. Physiol.: Cell Physiol. 283:C315-C326 (2002), thereby providing greater space around the cells for aqueous fluid to move to Schlemm's canal. Consequently, the broad statement Burke patent that blockers of Na^+/H^+ exchange, by themselves, do not lower IOP - is simply scientifically incorrect.

The Examiner has also rejected claim 46 under 35 USC § 103 as obvious, over Burke for the reasons stated in the previous argument, further in view of Scholtz *et al.* (US Patent No. 6,348,476). In making this rejection the Examiner relies on the teaching in Scholtz *et al.* that cariporide (not suggested in Burke) is an NHE inhibitor, and as such, cariporide could be used in the Burke invention to teach IOP reduction.

Of course, the Examiner's argument is misplaced for several reasons. Scholtz et al., issued February 19, 2002, is not prior art to Applicants' invention, which claims an effective

filing date (based upon the filing of International Application PCT/US00/12551) of May 8, 2000, which in turn claims a priority date of May 7, 1999. Nevertheless, Scholtz *et al.* deals with a blocker of Na^+/H^+ exchange for treatment of cardiovascular diseases, but prior to Applicants' own work there was no basis for presuming that blockers of Na^+/H^+ exchange would by themselves lower IOP. In fact, if one were to rely upon the Burke patent with which the Examiner suggests that Scholtz *et al.* be combined, one of ordinary skill in the art ould have understood that blockers of Na^+/H^+ exchange by themselves could not lower IOP.

Thus, the deficiencies of Burke cannot been met by Scholtz et al. to teach Applicants' invention. Each cited reference fails to teach the independent use of an Na^+/H^+ exchange inhibitor to reduce IOP. Thus, even when combined, they cannot teach the formation of a polymeric vesicle, or Applicants' use thereof; and they cannot render Applicants' invention obvious.

Accordingly, in light of the overwhelming differences between the cited prior art and that of the present invention, the present invention quite simply operates in a completely different manner from the prior art. Thus, the prior art fails to render Applicants' invention obvious, and Applicants respectfully request that in light of the foregoing, the rejection under 35 USC § 103 be reconsidered and withdrawn.

In sum, Applicants assert that all pending claims are in condition for allowance, and respectfully request that allowance be granted at the earliest date possible. Should the Examiner have any questions or comments regarding Applicants' amendments or response, she is asked to contact Applicants' undersigned representative at (215) 575-7034.

If there are any fees due in connection with the filing of this response, please charge the fees to our Deposit Account No. 50-0979.

Respectfully submitted,

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